



**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicant: Peter S. Linsley et al.  
Serial No.: 09/609,915  
Filed: July 3, 2000  
Docket: 30436.30USI2  
Title: SOLUBLE CTLA4 MUTANT MOLECULES AND USES THEREOF

**CERTIFICATE UNDER 37 CFR 1.8**

I hereby certify that this paper or fee is being deposited with the United States Postal Service as first class mail in an envelope addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231 on January 14, 2003.

By: 

Name: Tracy Truick

Assistant Commissioner for Patents  
Washington, D.C. 20231


Madam:

We are transmitting herewith the attached:

- ☒ Transmittal sheet, in duplicate, containing Certificate under 37 CFR 1.8.
- ☒ Supplemental Information Disclosure Statement (37 C.F.R. §1.97 (b)(3))
- ☒ Form 1449 (Information Disclosure Statement)
- ☒ Exhibits 115 -216
- ☒ Return postcard

Please charge any additional fees or credit overpayment to Deposit Account No. 50-0306. A duplicate of this sheet is enclosed.

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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

<b>Applicant:</b>	Peter S. Linsley et al.	<b>Examiner:</b>	Elaine-M. Lazar Wesley
<b>Serial No.:</b>	09/609,915	<b>Group Art Unit:</b>	1646
<b>Filed:</b>	July 3, 2000	<b>Docket No.:</b>	30436.30USI2
<b>Title:</b>	SOLUBLE CTLA4 MUTANT MOLECULES AND USES THEREOF		

**CERTIFICATE UNDER 37 CFR 1.8:**

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By: Tracy Bruick

55 South Lake Avenue  
Suite 710  
Pasadena, California 91101  
January 14, 2003

**SUPPLEMENTAL INFORMATION**  
**DISCLOSURE STATEMENT (37 C.F.R. § 1.97(b) 3))**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Dear Sir:

This Information Disclosure Statement is being filed herewith as a supplement to Applicant's April 2, 2001, Information Disclosure Statement which was submitted under 37 C.F.R. § 1.97 (b)(3) before the mailing date of the first Office Action on the merits. In accordance with 37 C.F.R. § 1.98(d), copies of Exhibits 115-216 as set forth in the Form 1449 are included herewith.

With regard to the above-identified application, the items of information listed on the enclosed Form 1449 are brought to the attention of the Examiner. They are as follows:

- Linsley, et al., 1991, *J.Exp.Med.* "CTLA-4 Is a Second Receptor for the B Cell Activation Antigen B7" 174:561-569. **(Exhibit 115)**

- Gimmi, et al., 1993, *Proc.Natl.Acad.Sci. USA* "Human T-Cell clonal anergy is induced by antigen presentation in the absence of B7 costimulation" 90:6586-6590. **(Exhibit 116)**
- Azuma et al., 1993 *Nature* "B70 antigen is a second ligand for CTLA-4 and CD28" 366:76-79. **(Exhibit 117)**
- Ronchese et al., 1994 *J.Exp.Med* "Mice Transgenic for a Soluble Form of Murine CTLA-4 Show Enhanced Expansion of Antigen-specific CD4 T Cells and Defective Antibody production In Vivo" 179:809-817. **(Exhibit 118)**
- Griggs et al., 1996 *J.Exp.Med* "The Relative Contribution of the CD28 and gp39 Costimulatory pathways in the Clonal Expansion and Pathgenic Acquisition of Self-reactive T Cells" 183:801-810. **(Exhibit 119)**
- Verwilghen et al., 1994 *J-Immunol.* Expression of Functional B& and CTLA4 on Rheumatoid Synovial T Cells" 153:1378-1385. **(Exhibit 120)**
- Blazar et al., 1994 *Blood* "In Vivo Blockade of CD28/CTLA4: Interaction With CTLA4-Ig Reduces Lethal Murine Graft-Versus-Host Disease Across the Major Histocompatibility Complex Barrier in Mice" 83:3815-3825. **(Exhibit 121)**
- Finck et al., *Science* "Treatment of Murine lupus with CTLA4Ig" 265:1225-1227. **(Exhibit 122)**
- Perrin et al., 1995 *J-Immunol* "Role of B7:CD28/CTLA4 in the Induction of Chronic Relapsing Experimental Allergic Encephalomyelitis" 154:1481-1490. **(Exhibit 123)**
- Pearson et al., 1994 *Transplantation* "Transplantation Tolerance Induced By CTLA4-Ig" 57:1701-1706. **(Exhibit 124)**
- Baliga et al., 1994 *Transplantation* "CTLA4Ig PROLONGS ALLOGRAFT SURVIVAL WHILE SUPPRESSING CELL-MEDIATED IMMUNITY" 58:1082-1090. **(Exhibit 125)**
- Tepper et al., 1994 *Transplantation Proceedings* "Tolerance Induction by soluble CTLA4 in a Mouse Skin Transplant Model" 26:3151-3154. **(Exhibit 126)**

- Perico et al., 1995 *Kidney International* "Toward novel antirejection strategies: In vivo immunosuppressive properties of CTLA4Ig" 47:241-246. **(Exhibit 127)**
- Finck et al., 1994 *Arthritis and Rheumatism* "Effects of CTLA4Ig in murine lupus" 37:S222. **(Exhibit 128)**
- Nishikawa et al., 1994 *Eur J. Immunol.* "Effect of CTLA-4 chimeric protein on rat autoimmune anti-glomerular basement membrane glomerulonephritis" 24:1249-1254. **(Exhibit 129)**
- Wallace et al., 1994 *Transplantation* "CTLA4ig treatment ameliorates the lethality of murine graft-versus-host disease across major histocompatibility complex barriers" 58:602-610. **(Exhibit 130)**
- Damle et al., *J. Immunol.* "Costimulation of T Lymphocytes with integrin Ligands intercellular Adhesion Molecule-1 or Vascular Cell Adhesion Molecule-1 Induces Functional Expression of CTLA-4, a Second Receptor for B7" 152:2686-2697. **(Exhibit 131)**
- Milich, et al., 1994 *J. Immunol* "Soluble CTLA-4 can suppress autoantibody production and elicit long term unresponsiveness in a novel transgenic model," 153:429-435. **(Exhibit 132)**
- Webb, et al., 1996 *Eur J. Immunol* "Prevention and amelioration of collagen-induced arthritis by blockade of the CD28 co-stimulatory pathway: requirement for both B7-1 and B7-2," 26:2320-2328. **(Exhibit 133)**
- Van Oosterhout, et al., 1997 *Am.J.Respir.Cell Mol.Biol.* "Murine CTLA4-IgG Treatment Inhibits Airway Eosinophilia and Hyperresponsiveness and Attenuates IgE Upregulation in a Murine Model of allergic Asthma," 17:386-392. **(Exhibit 134)**
- Abrams et al., 1999 *J-Clin-Invest* "CTLA4Ig-mediated blockade of T-cell costimulation in patients with psoriasis vulgaris. 103:1243-1252. **(Exhibit 135)**
- Ibrahim, et al., 1996 *Blood* "CTLAIG Inhibits Alloantibody Responses to Repeated Blood Transfusions," 88:4594-4600. **(Exhibit 136)**

- Lenschow, et al., 1995 *J Exp Med* "Differential Effects of anti-B7-1 and Anti-b&-2 Monoclonal Antibody Treatment on the Development of Diabetes in the Nonobese Diabetic Mouse," 181:1145-1155. **(Exhibit 137)**
- Lenschow, et al., 1992 *Science* "Long-Term Survival of Xenogeneic Pancreatic islet Grafts Induced by CTLA4Ig," 257:789-792. **(Exhibit 138)**
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- Wolfe, 1995 *Bailliere's Clinical Rheumatology* "The epidemiology of drug treatment failure in rheumatoid arthritis," 9:619-632. **(Exhibit 140)**
- Hochberg, et al., 1990 *Epidemiologic Reviews* "Epidemiology of Rheumatoid Arthritis: Update," 12:247-252. **(Exhibit 141)**
- Spector, 1990 *Epidemiology of Rheumatic Disease* "Rheumatoid Arthritis," 16:513-537. **(Exhibit 142)**
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- Parkin D, Jacoby A, McNamee P, 2000. "Treatment of multiple sclerosis with interferon  $\beta$ : an appraisal of cost-effectiveness and quality of life" *J Neurol Neurosurg Psychiatry*; 68: 144-149. **(Exhibit 147)**

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- Pearson TC, Alexander DZ, Winn KJ, Linsley PS, Lowry RP, Larsen CP, 1994. "Transplantation tolerance induced by CTLA4-Ig. *Transplantation*, 57:1701-1706. **(Exhibit 149)**
- Liao HX, Haynes BF, 1995. "Role of adhesion molecules in the pathogenesis of rheumatoid arthritis" *Rheum-Dis-Clin-Noth-Am*. Aug; 21(3): 715-40. **(Exhibit 150)**
- PCT No. WO 95/33770, December 14, 1995. **(Exhibit 151)**
- Thomas R, Quinn C. 1996. "Functional differentiation of dendritic cells in rheumatoid arthritis: role of CD86 in the synovium" *J-Immunol*. Apr 15; 156(8): 3074-86. **(Exhibit 152)**
- Verhoeven-AC; Boers-M; Tugwell-P, 1998. "Combination therapy in rheumatoid arthritis: updated systematic review" *Br-J-Rheumatol*. Jun;37 (6): 612-619 **(Exhibit 153)**
- Schiff M, 1997. "Emerging treatments for rheumatoid arthritis" *Am-J-Med*. Jan 27; 102 (1A): 11S-15S **(Exhibit 154)**
- Balsa A, Dixey J, Sansom DM, Maddison PJ, Hall ND, 1996. "Differential expression of the costimulatory molecules B7.1 (CD80) and B7.2 (CD86) in rheumatoid synovial tissue" *Br-J-Rheumatol*. Jan; 35(1): 33-7 **(Exhibit 155)**
- Ranheim Ea, Kipps Tj, 1994. "Elevated expression of CD80 (B7/BB1) and other accessory molecules on synovial fluid mononuclear cell subsets in rheumatoid arthritis" *Arthritis-Rheum*. Nov;37 (11): 1637-1647 **(Exhibit 156)**
- Freeman, GJ, Gribben JG, Boussiotis VA, et. al. 1993. "Cloning of B7-2: a CTLA-4 counter receptor that costimulates human T cell proliferation" *Science*, 262: 909-911. **(Exhibit 157)**
- Becker, J.C., March 8, 2001, Abstract and of Presentation of "A multi-center, randomized, double-blind, placebo controlled study to evaluate the safety and

preliminary clinical activity of multiple doses of CTLA4Ig and LEA29Y administration intravenously to subjects with rheumatoid arthritis,” presented at American College of Rheumatology Conference: “2001 Innovative Therapies in Autoimmune Diseases,” San Francisco, California **(Exhibit 158)**

- Aruffo, S., March 27, 2000, Presentation of “Approaches to Immune Regulation” at BIO 2000 in Boston, Mass. **(Exhibit 159)**
- Abrams, et al., September 4, 2000, *J.Exp.Med.* “Blockade of T Lymphocyte Costimulation with Cytotoxic T Lymphocyte- associated Antigen 4-Immunoglobulin (CTLA4Ig) Reverse the Cellular Pathology of Psoriatic plaques, Including the Activation of Keratinocytes, Dendritic Cells, and Endothelial Cells,” 192:681-693. **(Exhibit 160)**
- Srinivas, N.R. et al., December 1, 1995, *J.Pharmaceutical Sciences* “Pharmacokinetics and pharmacodynamics of CTLA4Ig (BMA-188667), a Novel Immunosuppressive Agent, in Monkeys following Multiple Doses,” 85:1-4. **(Exhibit 161)**
- Gandhi, et al., November 18, 1998, Abstract and Presentation of *PharmSci Supplement* “Physical and Chemical Characterization of BMS-224818, A Recombinant Fusion Protein,” in San Francisco, Ca. **(Exhibit 162)**
- Flesher, A.R., April 15, 1999, *Biological Process Sciences* Presentation of “Transgenic Production, A Comparative Study” at Bio 99 in Seattle, Washington. **(Exhibit 163)**
- Greve, K.F., May 9, 1996, *J Chromatography* “Capillary electrophoretic examination of underivatized oligosaccharide mixtures released from immunoglobulin G antibodies and CTLA4Ig fusion protein,” 749:237-245. **(Exhibit 164)**
- Srinivas, N.R., April 8, 1997, *Pharmaceutical Research* “Assessment of Dose Proportionality, Absolute Bioavailability, and Immunogenicity Response of CTLA4Ig (BMS-188667), a Novel Immunosuppressive Agent, Following Subcutaneous and Intravenous Administration to Rats,” 14:911-916. **(Exhibit 165)**
- Weiner, R.S., November 6-10, 1994, Abstract and Presentation of “Validation and PK Application of a Double Antibody Sandwich Enzyme Immunoassay For the

Quantitation of Human CTLA4Ig Fusion Protein (BMS-188667) In Mouse Serum,”  
(Exhibit 166)

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(Exhibit 168)
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- Webb, L.M.C. et al., July 23, 1996 *Eur J Immunol* “Prevention and amelioration of collagen-induced arthritis by blocade of the CE28 co-stimulatory pathway: requirement for both B7-1 and B7-2” 26:2320-2328. (Exhibit 172)
- Knoerzer, et al., May 5, 1995, *J Clin. Invest* “Collagen-induced Arthritis in the BB Rat Prevention of Disease by Treatment with CTLA4Ig” 96:987-993. (Exhibit 173)
- Larsen, et al., April 27, 2000, Abstract of “Prolongation of Renal Allograft Survival with Blockade of the CD28 Pathway Using A Novel Mutant CTLA4-IG Fusion Protein In Non-Human Primates,” in *Transplantation*, 69(8): #44, p. S123, Chicago, Il.  
(Exhibit 174)



- Larsen, et al., May 13-17, 2000, A Presentation of "Prolongation of Renal Allograft Survival With Blockade of the CD28 Pathway Using A Novel Mutant CTLA4-Ig Protein In Nonhuman Primates" at the American Society of Transplantation Meeting in Chicago, Il. **(Exhibit 175)**
- Larsen, Aug. 27-Sept.1, 2000, A Presentation of "Manipulation of Costimulatory Pathways: Targeting CD80 and CD86" at the XVII congress of the Transplantation Society in Rome, Italy. **(Exhibit 176)**
- Larsen, March 3-4, 2000, A Presentation of "Costimulation blockade: progress toward clinical application" at Canadian Society of Transplantation Annual Scientific meeting in Mont Tremblant, Quebec, Canada. **(Exhibit 177)**
- Larsen, Jan. 13-17, 2000, A Presentation of "Costimulation blockade: Progress toward clinical application" at the American Society of Transplantation Meeting in Las Croabas, Puerto Rico. **(Exhibit 178)**
- Hathcock, et al., August 30, 1993 *Science* "Identification of an Alternative CTLA-4 Ligand Costimulatory for t Cell Activation," 262:905-911. **(Exhibit 179)**
- Sfrikakis, et al., November 29, 1994 *Arthritis & Rheumatism* "CD28 Expression On T Cell Subsets in Vivo And CD28-Mediated T Cell Response In Vitro In Patients With Rheumatoid Arthritis," 38:649-654. **(Exhibit 180)**
- U.S. Patent No. 5,434,131, July 18, 1995. **(Exhibit 181)**
- PCT No. WO 02/02638 A2, January 10, 2002. **(Exhibit 182)**
- Lakkis, Fadi G., et al., "Blocking the CD28-B7 T Cell Costimulation Pathway Induces Long Term Cardiac Allograft Acceptance in the Absence of IL-4<sup>1</sup>," *The Journal of Immunology*, 1997, 158:2443-2448. **(Exhibit 183)**
- Pearson, Thomas C., et al., "ANALYSIS OF THE B7 COSTIMULATORY PATHWAY IN ALLOGRAFT REJECTION<sup>1</sup>," *Transplantation*, 1997, 63:1463-1469. **(Exhibit 184)**
- Pearson, Thomas C., et al., "TRANSPLANTATION TOLERANCE INDUCED BY CTLA4-Ig<sup>1</sup>," *Transplantation*, 1994, 57:1701-1706. **(Exhibit 185)**

- Alexander, Diane Z., "ANALYSIS OF A FUNCTIONAL ROLE FOR CHIMERISM IN CTLA4-Ig PLUS BONE MARROW-TREATED CARDIAC ALLOGRAFT RECIPIENTS," *Transplantation*, 1994, 91:416-418. **(Exhibit 186)**
- Larsen, Christian P., et al., "CD40-gp39 INTERACTIONS PLAY A CRITICAL ROLE DURING ALLOFRAFT REJECTION" *Transplantation*, 1996, 61:4-9. **(Exhibit 187)**
- Pearson, Thomas C., et al., "CTLA4-Ig PLUS BONE MARROW INDUCES LONG-TERM ALLOGRAFT SURVIVAL AND DONOR-SPECIFIC UNRESPONSIVENESS IN THE MURINE MODEL", *Transplantation*, 1996, 61:997-1004. **(Exhibit 188)**
- Weber, C.J., et al., "CTLA4-Ig Prolongs Survival of Microencapsulated Rabbit Islet Xenografts in Spontaneously Diabetic Nod Mice," *Transplantation Proceedings*, 1996, 28:821-823. **(Exhibit 189)**
- Alexander, D.Z., et al., "Analysis of effector mechanisms in murine cardiac allograft rejection," *Transplantation Immunology*, 1996, 4:46-48. **(Exhibit 190)**
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- Elwood, Eric T., et al., "Microchimerism and rejection in clinical transplantation," *The Lancet*, 1997, 349:1358-1360. **(Exhibit 192)**
- Larsen, Christian P., and Thomas C. Pearson., "The CD40 pathway in allograft rejection, acceptance, and tolerance," *Transplantation*, 1997, 9:641-647. **(Exhibit 193)**
- Konieczny, Bogumila T., et al., "IFN- $\gamma$  Critical for Long-Term Allograft Survival Induced by Blocking the CD28 and CD40 Ligand T Cell Costimulation Pathways<sup>1</sup>," *The Journal of Immunology*, 1998, 160:2059-2064. **(Exhibit 194)**
- Elwood, Eric T., et al., "PROLONGED ACCEPTANCE OF CONCORDANT AND DISCORDANT XENOGRAFTS WITH COMBINED CD40 AND CD28 PATHWAY BLOCKADE<sup>1</sup>," *Transplantation*, 1998, 65:1422-1428. **(Exhibit 195)**
- Niimi, Masanori, et al., "The Role of the CD40 Pathway in Alloantigen-Induced Hyporesponsiveness in Vivo<sup>1</sup>," *The Journal of Immunology*, 1998, 161:5331-5337. **(Exhibit 196)**

- Whitmire, Jason K., et al., "CD40-CD40 Ligand Costimulation Is Required for Generating Antiviral CD4 T Cell Responses But is Dispensable for CD8 T Cell Responses<sup>1</sup>," *The Journal of Immunology*, 1999,163:3194-3201. **(Exhibit 197)**
- Bingaman, Adam W., et al., "Vigorous Allograft Rejection in the Absence of Danger<sup>1</sup>," *Journal of Immunology*, 2000,164:3065-3071. **(Exhibit 198)**
- Bingaman, Adam W., et al., "TRANSPLANTATION OF THE BONE MARROW MICROENVIRONMENT LEADS TO HEMATOPOIETIC CHIMERISM WITHOUT CYTOREDUCTIVE CONDITIONING," *Transplantation*, 2000, 69:2491-2496. **(Exhibit 199)**
- Durham, Megan M., et al., "Cutting Edge: Administration of Anti-CD40 Ligand and Donor Bone Marrow Leads to Hemopoietic Chimerism and Donor-Specific Tolerance Without Cytoinductive Conditioning<sup>1</sup>," *Cutting Edge*, 2000,165:1-4. **(Exhibit 200)**
- Williams, Matthew A., et al., "Genetic Characterization of Strain Differences in the Ability to Mediate CD40/CD28-Independent Rejection of Skin Allografts<sup>1</sup>," *The Journal of Immunology*, 2000, 165: 6549-6857. **(Exhibit 201)**
- Bingaman, Adam W., et al., "The role of CD40L in T cell-dependent nitric oxide production by murine macrophages," *Transplant Immunology*, 2000, 8:195-202. **(Exhibit 202)**
- Adams, Andrew B., et al., "Costimulation Blockade, Busulfan, and Bone Marrow Promote Titratable Macrochimerism, Induce Transplantation Tolerance, and Correct Genetic Hemoglobinopathies with Minimal Myelosuppression<sup>1</sup>," *The Journal of Immunology*, 2001, 167:1103-1111. **(Exhibit 203)**
- Meng, L., "Blockade of the CD40 Pathway Fails to Prevent CD8 T Cell-Mediated Intestinal Allograft Rejection," *Transplantation Proceedings*, 2001, 33:418-420. **(Exhibit 204)**
- Guo, Zhong., et al., "CD8 T CELL-MEDIATED REJECTION OF INTESTINAL ALLOGRAFTS IS RESISTANT TO INHIBITION OF THE CD40/CD154

COSTIMULATORY PATHWAY,” *Transplantation*, 2001, 71:1351-1354.

**(Exhibit 205)**

- Ha, Jongwon., et al., “Aggressive skin allograft rejection in CD28<sup>-/-</sup> mice independent of the CD40/CD40L costimulatory pathway,” *Transplant Immunology*, 2001, 9:13-17.

**(Exhibit 206)**

- Bingaman, Adam W., et al., “ANALYSIS OF THE CD40 AND CD28 PATHWAYS ON ALLOIMMUNE RESPONSES BY CD4<sup>+</sup> T CELLS IN VIVO<sup>1</sup>,” *Transplantation*, 2001, 72:1286-1292. **(Exhibit 207)**

- Adams, Andrew B., et al., “Calcineurin Inhibitor- Free CD28 Blockade-Based Protocol Protects Allogeneic Islets in Nonhuman Primates,” *Diabetes*, 2002, 51:265-270.

**(Exhibit 208)**

- Whelchel, JD., et al. “Evolving Strategies in immunosuppressive Therapy: The Emory Experience,” *Clinical Transplants*, 1996, 20:249-255 **(Exhibit 209)**

- Ritichie, SC., et al., “Regulation of Immunostimulatory function and B7 molecule expression on murine dendritic cells,” *Journal of Cellular Biochemistry*, 1995, 21A:C1-215 **(Exhibit 210)**

- Alexander, DZ., et al., “Analysis of the mechanisms of CTLA4-Ig plus bone marrow induced transplantation tolerance,” *Journal of Cellular Biochemistry*, 1995, 21A:C1-301 **(Exhibit 211)**

- Alexander, DZ., et al., “CTLA4-Ig induced transplantation tolerance: analysis of donor cell chimerism,” *Surgical Forum*, 1994, 45:402-403 **(Exhibit 212)**

- Pearson, TC., et al., “CTLA4-Ig plus bone marrow induces transplantation tolerance in the murine model,” *Journal of Cellular Biochemistry*, 1995, 21A:C1-327

**(Exhibit 213)**

- Lakkis, FG., et al., “CTLA4Ig induces long-term cardiac allograft survival in the absence of interleukin-4,” *Journal of the American Society of Nephrology*, 1996, 7:A3204 **(Exhibit 214)**

- L104EA29Y (Figure 24, of the subject application) was provided to researchers at Emory University, subject to use restrictions and confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000, for use in animal studies in the U.S.
- L104EA29Y (Figure 24 of the subject application) has been the subject of human clinical trials under the direction and control of Bristol-Myers Squibb Company. L104EA29Y was given to investigators who were involved in the clinical trials subject to use restrictions and confidentiality by agreement. L104EA29Y was administered intravenously to human patients in clinical trials.
  - L104EA29Y was first administered intravenously to a human patient as early as November 30, 1998 in Scotland.
  - L104EA29Y was first administered intravenously to a human patient as early as April 24, 1999 in the United States.
- A letter dated July 9, 1998 including a report, submitted to the U.S. Food and Drug Administration in connection with an Investigational New Drug (IND) application, is enclosed as **Exhibit 215**.
  - The letter and report are confidential and were provided confidentially, pursuant to 21 C.F.R. §20.111 or §21 C.F.R. §312.130, to the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration in connection with the Investigational New Drug Application.
  - The enclosed letter and report are redacted versions of what were sent to the U.S. Food and Drug Administration.
  - The report contained the sequence for BMS-224818 (Figure 3 at page 13 of Exhibit 215), which differs from CTLA4Ig at two amino acid residues, Leu<sub>104</sub>-Glu and Ala<sub>29</sub>-Tyr (Exhibit 215 at page 2).
- An Investigator Brochure dated January 26, 1999 is enclosed as **Exhibit 216**.
  - The Investigator Brochure is confidential and was provided to investigators who were involved in the clinical trials and subject to confidentiality by agreement,

more than one year before the priority date of the subject application, i.e. May 26, 2000.

- The enclosed Investigator Brochure is a redacted version of what was sent to investigators.
- The Investigator Brochure contained a text description and a schematic representation of LEA29Y (Figure 1 at page 6 of Exhibit 216), but not the sequence of L104EA29Y (Figure 24, of the subject application).

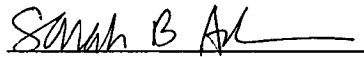
No representation is made that a reference is "prior art" within the meaning of 35 U.S.C. §§ 102 and 103 and Applicants reserve the right, pursuant to 37 C.F.R. § 1.131 or otherwise, to establish that the references are not "prior art." Applicants wish to reiterate that the documents and information above were not at the time of filing publicly available since they were provided under confidentiality agreements.

Consideration of the items listed is respectfully requested. Applicants invite the Patent Office to request additional information if necessary. Pursuant to the provisions of M.P.E.P. 609, it is requested that the Examiner return a copy of the attached Form 1449, marked as being considered and initialed by the Examiner, to the undersigned with the next official communication.

Peter S. Linsley et al.  
U.S. Serial No. 09/609,915  
Filed: July 3, 2000  
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No fee is deemed necessary in connection with the filing of this Information Disclosure Statement. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-0306.

Respectfully submitted,



Sarah B. Adriano  
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FORM 1449\*

**INFORMATION DISCLOSURE STATEMENT  
IN AN APPLICATION**

(Use several sheets if necessary)

Docket Number

30436.30USI2

Application Number

09/609,915

Applicant

Peter S. Linsley et al.

Filing Date

July 3, 2000

Group Art Unit

1646

**U.S. PATENT DOCUMENTS**

EXAMINER INITIAL	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLAS S	FILING DATE IF APPROPRIATE
	5,434,131 (Exhibit 181)	7/18/95	Linsley et al.			5/26/93

**FOREIGN PATENT DOCUMENTS**

DOCUMENT NO.	DATE	COUNTRY	CLASS	SUBCLAS S	TRANSLATION	
					YES	NO
WO 95/33770 (Exhibit 151)	12/14/95	PCT				X
WO 02/02638 A2 (Exhibit 182)	1/10/02	PCT				X

**OTHER DOCUMENTS** (Including Author, Title, Date, Pertinent Pages, Etc.)

	Linsley, et al., 1991, <i>J.Exp.Med.</i> "CTLA-4 Is a Second Receptor for the B Cell Activation Antigen B7" 174:561-569. (Exhibit 115)
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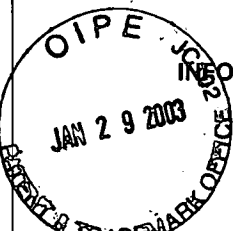
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	Applicant	
	Peter S. Linsley et al.	
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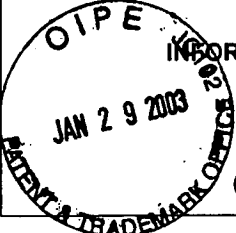
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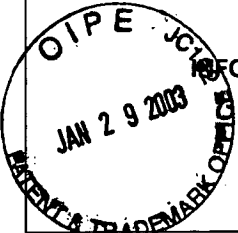
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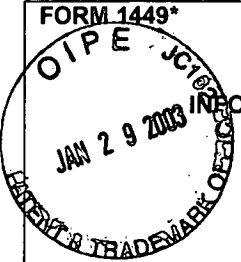
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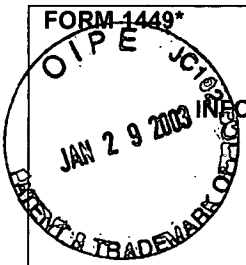
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	Lakkis, FG., et al., "CTLA4Ig induces long-term cardiac allograft survival in the absence of interleukin-4," <i>Journal of the American Society of Nephrology</i> , 1996, 7:A3204 (Exhibit 214)
	L104EA29Y (Figure 24, of the subject application) was provided to researchers at Emory University, subject to use restrictions and confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000, for use in animal studies in the U.S.
	L104EA29Y (Figure 24 of the subject application) has been the subject of human clinical trials under the direction and control of Bristol-Myers Squibb Company. L104EA29Y was given to investigators who were involved in the clinical trials subject to use restrictions and confidentiality by agreement. L104EA29Y was administered intravenously to human patients in clinical trials.

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.	

\*Substitute Disclosure Statement Form (PTO-1449) Patent and Trademark Office, U.S. DEPARTMENT OF COMMERCE

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<b>FORM 1449*</b>  <b>INFORMATION DISCLOSURE STATEMENT IN AN APPLICATION</b> (Use several sheets if necessary)	<b>Docket Number</b> 30436.30USI2	<b>Application Number</b> 09/609,915
	<b>Applicant</b> Peter S. Linsley et al.	
	<b>Filing Date</b> July 3, 2000	<b>Group Art Unit</b> 1646

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)		
		L104EA29Y was first administered intravenously to a human patient as early as November 30, 1998 in Scotland.
		L104EA29Y was first administered intravenously to a human patient as early as April 24, 1999 in the United States.
		A letter dated July 9, 1998 including a report, submitted to the U.S. Food and Drug Administration in connection with an Investigational New Drug (IND) application, is enclosed as <b>Exhibit 215</b> .
		The letter and report are confidential and were provided confidentially, pursuant to 21 C.F.R. §20.111 or §21 C.F.R. §312.130, to the Center for Biologics Evaluation and Research at the U.S. Food and Drug Administration in connection with the Investigational New Drug Application.
		The enclosed letter and report are redacted versions of what were sent to the U.S. Food and Drug Administration.
		The report contained the sequence for BMS-224818 (Figure 3 at page 13 of Exhibit 171), which differs from CTLA4Ig at two amino acid residues, Leu104-Glu and Ala29-Tyr (Exhibit 171 at page 2).
		An Investigator Brochure dated January 26, 1999 is enclosed as <b>Exhibit 216</b> .
		The Investigator Brochure is confidential and was provided to investigators who were involved in the clinical trials and subject to confidentiality by agreement, more than one year before the priority date of the subject application, i.e. May 26, 2000.
		The enclosed Investigator Brochure is a redacted version of what was sent to investigators.
		The Investigator Brochure contained a text description and a schematic representation of LEA29Y (Figure 1 at page 6 of Exhibit 172), but not the sequence of L104EA29Y (Figure 24, of the subject application).

<b>EXAMINER</b>	<b>DATE CONSIDERED</b>
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form for next communication to the Applicant.	
*Substitute Disclosure Statement Form (PTO-1449) Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE	